REMARKS

I. Status of the Claims

With this response, claims 9, 10, 24-40, 42-43, 49-60, 63-66, and 68-75 are pending in the present application and are under examination. Claims 1-8, 11-23, 41, 44-48, 61-62, and 67 have been canceled.

II. Claim Rejection, 35 U.S.C. 103(a)

Claims 9, 10, 24-29, 33, 39, 40, 42, 43, 49-52, 54-60, 63-66, and 68-75 have been rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Shiver *et al.* (WO98/34640), Schwartz *et al.* (1992, J. Virol. 66:7176-82), Schneider *et al.* (1997, J. Virol. 71:4892-4903), Haas *et al.* (1996, Current Biology 6:315-24), Persson *et al.* (1998, Biologicals 26:255-65), and Novitsky *et al.* (1998, direct submission to GenBank, 12/3/1998).

Applicants respectfully traverse the rejection and its supporting remarks. The Examiner has still not established a *prima facie* case of obviousness. The Examiner has identified Novitsky as teaching the same starting point as used by the inventors of the present invention, i.e., AF110965 and AF110967. In addition, the Examiner has cited to references that are asserted to teach the techniques used by the present inventors to arrive at the presently claimed invention. But the present claims are not directed to a method of generating an optimized HIV gene starting from AF110965 or AF110967 and generally applying the techniques of codon optimization and removal of instability elements. Rather, the pending claims are directed to specific sequences that the inventors generated using specifically selected techniques. The Examiner has not demonstrated that one of skill in the art would arrive at the presently claimed SEQ ID NOs: 3 and 4 based upon the teachings cited.

First, as indicated in the attached reference Novitsky *et al.* (1999, J. Virol. 73:4427-4432), AF110965 and AF110967 were part of a panel of twenty three HIV isolated that had been sequenced. By contrast, the present application and the present claims are based upon only two of

the twenty three sequences. Thus, the inventors presumably applied their expertise to review these sequences and selected two. The Examiner has not provided any reason why one of skill in the art would have been motivated to select these two sequences from among the twenty three submitted at the same time, much less the large number of HIV sequences that must have been available as of the priority date. To establish a prima facie case of obviousness, the Examiner would need to establish that one of skill in the art would have some reason to select these two sequences from at least the twenty-three in the 1999 Novitsky paper.

Next, the Examiner has asserted that Shiver *et al.* teaches codon optimization based upon "preferred human codons". However, there are a number of methods available for codon optimization. For example, one of skill in the art could look at relative codon frequencies across all human genes. Alternatively, one of skill in the art could look at the relative codon frequencies only for "highly expressed" human genes. However, "highly expressed" is a relative concept, different people will generate different sets of "preferred human codons". The inventors of the present invention selected a particular codon optimization based upon a set of criteria. The Examiner has not demonstrated that the codon optimization of Shiver *et al.* would produce the sequences of SEQ ID NOs 3 and 4. Even if Shiver *et al.* did apply a codon optimization that could approximate the assembly of SEQ ID NOs 3 and 4, Shiver *et al.* would still have to provide a reason why that particular codon optimization was applied over any other, otherwise the Examiner would merely be selecting Shiver *et al.* in hindsight based upon the inventors' teaching of the codon optimization technique that they selected.

Finally, the Examiner appears to have acknowledged that Shiver *et al.* does not teach the type of additional modification applied by the inventors as there appears to be no removal of the ATTTA (AUUUA) evidenced in Figure 5, which shows the additional modifications by the inventors after codon optimization. This again highlights that there are a number of other modifications available besides codon optimization to one of skill in the art to improve the expression of HIV polypeptides, specifically the GAG peptides of the present invention. The Examiner has not demonstrated that application of the elimination of inhibitory/instability elements

as taught by either Schneider *et al.* or by Schwartz *et al.* would produce the sequences of SEQ ID NOs 3 and 4. Schwartz *et al.* in Figure 4 only show four instability elements. Schwartz *et al.* in Figure 6 show an additional region where instability elements are found, but the actual elements are not expressly defined. Schneider *et al.* in Figure 1, shows the same four elements as in Schwartz *et al.* with an additional six elements that likely correspond to the additional region where instability elements are found as identified in Schwartz *et al.* The additional six elements only extend to nucleotide +1029 (where the A of the starting ATG is +1). By contrast, as shown by Figures 5 and 6 of the present application, the inventors made three mutations that occurred further downstream in the GAG gene to generate each of SEQ ID NOs 3 and 4. Thus, one of skill in the art making the modifications taught by Shiver *et al.*, Schwartz *et al.*, and Schneider *et al.* could not have generated the presently claimed SEQ ID NOs 3 and 4.

Thus, Applicants respectfully assert that the Examiner has not established a *prima facie* case of obviousness as the Examiner has not provided any reason why one of skill in the art would have selected the two out of the twenty three sequences selected by the inventors from Novitsky *et al.* (1999), and why one of skill in the art would have selected the codon optimization technique selected by the inventors, or why one of skill in the art would select the modifications taught by Shiver *et al.*, Schwartz *et al.*, and Schneider *et al.* and would be able to produce SEQ ID NOs 3 and 4 as presently claimed. Furthermore, even if the Examiner could provide such reasons, the Examiner has not demonstrated that application of the modifications of Shiver *et al.*, Schwartz *et al.*, and Schneider *et al.* would even result in the presently claimed SEQ ID NOs 3 and 4, especially in light of the fact as discussed above that these two sequences each contain three mutations in regions that neither Schwartz *et al.* nor Schneider *et al.* suggested making mutations.

Thus, Applicants respectfully respect that the Examiner withdraw the rejection of the presently pending claims.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing Docket No. 223002109700. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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